REMARKS

Applicant traverses the rejections of claims 2, 7, 8, 10 and 21-25 as being unpatentable as obvious under 35 U.S.C. 103 over Boyce et al. U.S. Patent Number 6,294,187 in view of the combination of Sander et al. 5,356,629 and Breitbart et al. U.S. Patent Number 5,700,289.

The Boyce '187 patent simply teaches a shaped hardened osteoimplant bone composition formed of compressed elongated bone particles and not powdered demineralized individual bone particles as argued by the Examiner. The Boyce bone composition has a bulk density greater than about 0.7 g/cm^3 and a wet composite strength substantially exceeding 3MPa and the bone particles range in average particle size from about 0.05 to about 1.2 cm in size and possess an average median length to median thickness of from about 1:1 to about 3:1. The particles are obtained by milling or shaving the surface of an entire bone with at least 60%, preferably 90% of the bone particles being elongated. These elongated particles possess a medium length from about 2 to 200 mm and more preferably from 10 to about 100mm. As noted in the Examples; the bone particles were mixed with different solutions such as glycerol (Examples 1, 12), ethanol (Examples 5, 6, 7, 8), heated water (Examples 9, 10, 11), saline (Example 4(and cross linked with formalin (Examples 2 and 3). There is no teaching of the carrier of the present invention, the bone particle size, the hydrogel used or the weight of the same and weight of the same in the aqueous solution, or any concentration of cellular material (Boyce et al '187 being a solid and having no viscosity). Applicant would point out that the use of hydrogels, dextran, CMC and HPMC are disclosed only as a thickener when water and/or glycerol are used as the wetting agent for forming the slurry. These hydrogels are used to suspend and keep the bone particles separate during the application of the compression forces to form the solid structure and do not act as a carrier for the bone particles.

Compressive forces typically ranging from about 2,500 to 60,000 psi are applied to bone particles in a mold to produce a hard chalk-like material. Chitosan is only noted as an adhesive for the demineralized bone particles and is incidentally found as one of a 30+ line list of suitable adhesives (col. 8, lns. 13-40) or as a thickener to preclude premature bone particle separation and improve suspension keeping characteristics of the composition (col. 10, lns. 58-57 and col. 11, lns. 1-10). This is used to keep the bone particles separate during application of the compressive forces to form the solid structure and do not act as a carrier for the bone products which is then directly applied to the wound site. The reference cannot be combined with Sander '629 and/or Breitbart et al. '289 and does not teach or suggest the composition of the present invention in connection with the teachings of the Sander '629 patent and/or Breitbart et al. 289.

The Sander et al. '629 reference discloses the making of a rigid gel in the nature of a bone cement to fill defects in bone by mixing biocompatible particles preferably polymethylmethacrylate coated with polyhydroxyethylmethacrylate (Examples 1 , 2 and 5 - 10) or particles of glycolide-lactide copolymer (Examples 3 and 4) in a matrix to obtain a molded semi-solid mass which can be suitably worked for implantation into bone. Alternatively, the matrix or carrier for the biocompatible particles can be cellulose, ether, collagen or hyaluronic acid (HA). Nonbioabsorbable material disclosed in the specification which can be used to form the biocompatible particles used in the matrix can be derived from xenograft bone, homologous bone, autogenous bone, hydroxyapatite and polymethylmethacrylate, the preferred nonbioabsorbable material as well as other materials. The weight of the nonbioabsorbable material in the wetted composition of Sander et al '629 runs from 35% to 75% (Dry weight 64% to 94%); to most preferably 45% to 60% (Dry weight 73% to 92%) with the more preferred weight being 40% to 70% (Dry weight 82% to 90%)(Col 4 lns 21 - 30).

There is no disclosure of demineralized bone used as the nonbioabsorbable material, in Sander et al '629 and demineralized bone is used as an additive in the nature of a bioactive agent. It is noted in Col. 4 ln 40 to Col. 5 ln 17 that a bioactive substance can be introduced into the composition, the preferred substance being polymethylmethacrylate. This bioactive substance can be an osteogenic agent such as demineralized bone powder, in addition to morselized cancellous bone, aspirated bone marrow and other autogenous bone sources. As previously noted demineralized bone powder **is an additive of undetermined amount** and is included in a general laundry list and is not taught to be the biocompatible material, but rather an osteogenic agent.

In Examples 1-6 polymethylmethacrylate particles were coated with polyhydroxyethylmethacrylate carboxymethylcellulose or methylcellulose and water and in Examples 7-10, particles of polymethylmethacrylate coated with polyhydroxethylmethacrylate, the preferred nonbioabsorbable material were mixed with a matrix **HA having a molecular weight of about six hundred thousand Daltons.** Indeed **in all of the Examples no bone material of any type is used.** The use of demineralized bone in the present invention results in the osteoinductive medically beneficial bone repair of the present invention.

Sander et al. '629 has a matrix ranging from 6% to 36% with 64% polymethylmethacrylate crystals (if one were to substitute demineralized bone material for the polymethylmethacrylate coated with polyhydroxyethacrylate of Sander et al '629, which substitution is not taught or suggested by this reference) or you would have a completely different material.

Sander et al. '629 does not teach or obviate the present invention alone or combined with the other cited references. Use of (1) demineralized bone material as the nonbioabsorbable material and as a major component of the composition or (2) an equivalent biocompatible material weight, (3) a

phosphate buffer to neutralize the composition, and (4) the addition of cellular material at a concentration of 10^5 to 10^8 per cc of the carrier is not taught or disclosed. Furthermore Sander et al is not osteogenic relying on antigenic response.

The '629 reference does not suggest using demineralized bone together in a buffered isotonic salt carrier with a neutral osmolality or that such a combination is osteoinductive and medically beneficial in the repair of bone tissue. The Examiner's inference that the '629 patent teaches that the composition can comprise living cells such as erythrocytes, leucocytes and endothelial cells and that the pH of the composition is approximately 6.8-7.4 is not based on the teachings of the '629 patent and is a hind site supposition.

The patent to Breitbart et al. '289 is directed toward periosteum cells seeded into a matrix (preferably a synthetic polymer) for repair of the bone defect. The '289 patent does disclose stem cells, chondrocytes and mesenchyma cells as follows: Col. 2, lns. 45-60, prior art showing the use of autologous cells and chondrocytes attaching to hydroxyapatite. Col. 4, lns. 25-30 discloses the use of periosteum which consists of multipotent mesodermal cells. Col. 14, ln. 60 claim refers to periosteum cells seeded in biocompatible matrix. In regard to the disclosure of alginate and chitosan, in col. 6, lns. 35-40 a large laundry list of potential natural and synthetic polymers which can be used to form a fibrous or sponge-like matrix for the seeding of cell includes alginate. It is quite apparent that the matrix is solid as it is preferably made of hydroxyapatite, tricalcium phosphate, sterilized bone or metal alloy. In col. 10, lns. 5-10, the hydrogel which is noted as being cross linked to form a three dimensional open-lattice structure includes alginate. In col. 10, lns. 50-55 alginate is disclosed as being used for hybridonia cell encapsulation, which has nothing to do with the present invention. In col. 11, lns. 35-40, chitosan is only noted for being one of a number of polycations

which complex and stabilize the polymer hydrogel into a semipermeable surface membrane. Various examples are noted and it is off handedly noted, that there exists natural polycations such as the polysaccharide chitosan.

Furthermore, none of the cited references disclose the additives of cells at a concentration of 10^5 - 10^8 per cc of carrier or a specific amount of growth factor added 10cc of carrier.

In cases which are similar to the present circumstances, the courts have ruled that beyond looking at the prior art to determine if it suggests doing what the inventor has done, one must consider if the prior art provides an expectation of succeeding in the endeavor. *In re Dow Chem.,* 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988), "Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure." Id. As noted by the court in the case of *In re Clinton,* "Obviousness does not require absolute predictability, but a reasonable expectation of success is necessary." *In re Clinton,* 527 F.2d 1226, 1228, 188 U.S.P.Q. 365, 367 (C.C.P.A.1976).

As noted by the Court in the case of *In re Gordon,* the mere fact that a prior art reference could be modified to achieve the claimed invention does not make the modification obvious unless the prior art suggested the desirability of the modification. *In re Gordon,* 733 F.2d 900, 902, 221 U.S.P.Q. 1125, 1127 (Fed. Cir.1984); see also *In re Laskowski,* 871 F.2d 115, 117, 10 U.S.P.Q.2d 1397, 1398 (Fed. Cir. 1989), and *Ex parte Levengood,* 28 U.S.P.Q.2d 1300, 1302 (Bd. Pat. App. & Int. 1993). Applicants respectfully submit that is there is not any suggestion showing the desirability to arrive at the claimed structure of the present invention.

The court in *Minnesota Mining & Manufacturing Co. v. Johnson &Johnson Orthopaedics, Inc.,* 24 USPQ2d 1321 (Fed. Cir 1992) held that: "Although [a patent's] specific claims are subsumed

in [a prior art reference's] generalized disclosure..., this is not literal identity." The *Minnesota* court held that the reference's ranges were so broad as to be meaningless, and provided no guidance on how to construct a product with the patented invention's benefits. The court in *In re Baird,* 29 USPQ2d 1550 (Fed. Cir. 1994) held that "The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious." The *Baird* court further held that a disclosure to numerous compounds does not render obvious a claim to three compounds, particularly when that disclosure indicates a preference leading away from the claimed compounds.

None of the cited references singularly or in combination teach or obviate the present invention. The Examiner has engaged in hind site and conjecture to combine the sited prior art references against the present invention.

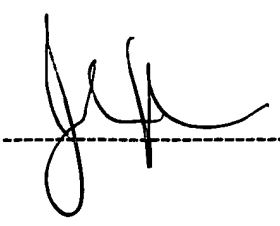
Two terminal disclaimers are filed with this Amendment to overcome the obviousness-type double patenting rejection. One terminal disclaimer is filed with respect to U.S. Patent Number 6,326,018. The other terminal disclaimer is filed with respect to U.S. Patent Number RE38,522. The '522 reissue is a reissue of U.S. Patent Number 6,030,635 which has been surrendered.

If any additional charges are required, please charge Deposit Account Number 07-1340.

It is respectfully requested that the arguments and amendments present in the present application in condition for favorable reexamination and that the application be passed to issue.

Respectfully submitted,

GIPPLE & HALE



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